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Langerhans Cell Histiocytosis in Children Under 2 Years of Age

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This is a retrospective study of 55 children under the age of 2 years diagnosed with Langerhans cell histiocytosis (LCH). They were classified according to age and organ function and dysfunction following Lahey's criteria. The studied population was divided into four groups by age of diagnosis (0–6, 7–12, 13–18, and 19–24 months). Statistical analysis showed no significant difference in outcome between age groups, although the population under 6 months had a 81.3% fatality rate. The presence of organ dysfunction was a major cause of death in all age groups, being statistically significant in outcome ($P > 0.005$) compared with patients without organ dysfunction. The presence of thrombocytopenia and/or respiratory dysfunction was also highly associated with a fatal outcome. In the surviving population, no second malignancies have been reported. The late secondary effects of therapy include endocrine, orofacial, and osseous pathologies.

Key words: Langerhans cell histiocytosis, histiocytosis X, childhood histiocytosis, thrombocytopenia, organ dysfunction, late sequelae

Introduction

Langerhans cell histiocytosis (LCH), also referred to as histiocytosis X (HX) [1,2], ranges in its clinical presentation from a single osteolytic lesion to multiple organ/system involvement [3–12]. The pathognomonic cell is the Langerhans cell (LC), a skin phagocyte belonging to the monocyte-phagocytic system [3,13]. Whether its origin is immunologic or proliferative remains controversial. The presence of Birbeck granules in EM and T-6 antigenic determinants is required features for a definitive diagnosis of LCH [1,2]. A variety of therapeutic agents have been used with varying degrees of success [8,23–25]. Among them, the combination of vinca alkaloids, steroids, and alkylating agents has been widely used in the past, with the recent addition of etoposide (VP-16) to chemotherapeutic regimens [26–28].

Included among the unfavorable prognostic factors for LCH are age and dissemination/organ malfunction [5–8]. This report concerns itself solely with patients under 2 years of age at diagnosis, the role of age at diagnosis, the role of dissemination/organ dysfunction, and the response to conventional therapy, outcome, complications, and late sequelae.

Materials and Methods

We reviewed the medical records of 65 patients under 2 years of age who were newly diagnosed with LCH from 1978 to 1988 and were followed up at least 5 years after diagnosis (December 93) at the Instituto Nacional de Pediatría (National Institute of Pediatrics) in Mexico City, Mexico. Ten patients were lost to follow-up. Patients were classified according to Lahey's criteria for organ dysfunction [6,29] and were placed into four groups according to age for the study: group A (0–6 months), group B (7–12 months), group C (13–18 months), and group D (19–24 months). Tables I–IV list the demographics of the four age-related study groups.

The following parameters were evaluated: age when signs and symptoms initially manifested, age at diagnosis, abscence or presence of organ dysfunction, extent of organ dysfunction, involvement of other organs, histologic report, therapy utilized, length of therapy, response of therapy, outcome, cause of death, and late sequelae in the surviving population.

Lahey's criteria for organ dysfunction are as follows [6,29]: (1) hematopoietic dysfunction: anemia (Hgb <10 g/dl not due to iron deficiency or infection) and/or leukopenia (leukocyte count, <4,000 cells/mm^3), and/or neutropenia (neutrophil count <1,500 cells/mm^3), and/or

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TABLE I. Group A, 0–6 Months

Pt. #	Age S & S noted (mo)	Age dx (mo)	Presence of organ dysfunction	Involvement of other organs	Biopsy	Therapy	Length of therapy	Actual status	Late sequelae
1	0	2	Y; P	S	UH(S)	VCR/MTX/PDN	2 mo	Death; P dysfunction	
2	0	21	Y; H(a)	B (skull/mandible), S	FH(B)	Thymosin	2 yr	Alive; 15 yo	Oral cavities
						VBL/PDN/MTX/CLB	2 yr		
3	2	5	Y; H(a), L, P	B (skull/mandible), LN	UH(LN)	VCR/CYT/MPDN	2 mo	Death; P dysfunction	
4	3	7	Y; H(a)	B (skull), S, ST,	UH(S)	VCR/MTX/MPDN/CLB	2 yr	Alive; 15 yo	Hypoacusia
5	3	3	N	Ot, S	FH(S)	VBL/PDN/VCR/MTX	1 mo	Death; progressive disease	
6	3	11	N	B (skull, mandible), G, Ot, S	DH(S)	VBL/PDN/MTX/CLB	10 mo	Death; disease progression	
						CYT/VBL/PDN/PCZ		P, H, L dysfunction	
						VP-16/PDN/CLB			
7	4	6	Y; H(a), P	LN, Maln, S	UH(LN)	VBL/PDN/MTX	1 mo	Death; pneumonia	
8	4	18	Y; H(a), L	B (skull), GI, LN, Maln, Ot, S	UH(LN)	VCR/PDN/MTX	3 mo	Death; H dysfunction & sepsis	
9	4	11	Y; H(a), L	Ot, S	UH(LN)	VBL/PDN/CLB/MTX	5 mo	Death; progressive disease to G.I., gram-negative rod sepsis	
10	4	4	Y; H(l), L	Ot, S	UH(LN)	VCR/PDN/MTX/CLB	1 mo	Death; P dysfunction	
11	5	7	Y; H(a,t), L, P	Maln, S	UH(S)	VCR/PDN/CLB	2 mo	Death; H & P dysfunction GI infiltration, persistent diarrhea	
12	6	14	Y; H(a,l,t), L	LN, Ot, S	DH(S)	CYT/VBL/PDN/PCZ	8 mo	Death; H dysfunction, progressed to P dysfunction & sepsis, gram-positive cocci	
13	6	10	Y; H(a)	B (skull), D.I.	FH(LN)	VBL/PDN/MTX/CLB	2 yr	Alive; 13 yo	D.I.
14	6	10	Y; L	LN, Ot, S	UH(LN)	VCR/PDN/VBL/CLB/MTX	4 mo	Death; H & P dysfunction	
15	6	12	Y; H(a), L	B (skull), GI, LN, Ot, S	UH(LN)	VBL/PDN	2 mo	Death; pnemonia	
16	6	10	N	B (skull), LN, S, ST	n/a	VCR/PDN/MTX/CLB	9 mo	Death; acute diarrhea with neutropenia/sepsis	

H = hematologic dysfunction; L = hepatic dysfunction; P = pulmonary dysfunction; (a) = anemia; (t) = thrombocytopenia; (l) = leukopenia; B = bone; D.I. = diabetes insipidus; G = gums; GI = gastrointestinal; LN = lymph node; Maln = moderate/severe malnutrition; Ot = otitis; S = skin; ST = soft tissue; FH = favorable histology; UH = unfavorable histology; DH = descriptive histology; PDN = prednisone; VBL = vinblastine; VCR = vincristine; CLB = chlorambucil; MTX = methotrexate; PCZ = procarbazine; VP-16 = etoposide; CYT = cyclophosphamide; Ara-C = cytarabine; ATG = anti-thymocyte globulin; XRT = radiation therapy; yo = years old; S & S = signs and symptoms; dx = diagnosed.

TABLE II. Group B, 7–12 Months

Pt. #	Age S & S noted (mo)	Age dx (mo)	Presence of organ dysfunction	Involvement of other organs	Biopsy	Therapy	Length of therapy	Actual status	Late sequelae
1	7	19	N	B (palate/iliac), ST	n/a	VBL/PDN/CLB/MTX	18 mo	Alive; 8 yo	Orthodontic pathology, low stature
2	7	12	Y; H(a), P	B (skull), Ot, S	DH(S)	VBL/JPDN	2 mo	Death; sepsis *P. aeruginosa*	
3	7	11	Y; H(a), L	B (long bones, skull, ribs, vertebrae), S	DH(S)	VBL/PDN	2 mo	Death; H, L, P dysfunction	
4	8	24	Y; L, P	B (skull), LN, Ot, S	FH(LN)	VBL/PDN/MTX/CLB	18 mo	Alive; 14 yo	D.I.
5	9	10	Y; H(a), L, P	LN, S	UH(S)	VBL/PDN/CLB	1 mo	Death; H & L dysfunction	
6	9	10	N	B (skull, femur, ribs), LN, Ot, S, ST	FH(LN)	VBL/PDN/MTX/CLB	18 mo	Alive; 13 yo	Café-au-lait spots, occipital hyperdense lesion in CT scan
7	9	12	Y; H(a), L	B (humerus/radii), LN, S	UH(LN)	VBL/PDN/MTX/CLB	6 mo	Death; H & L dysfunction & *Salmonella* sepsis	
8	10	37	N	B (skull, ribs), D.I., S	DH(S)	CYT/VBL/PCZ/PDN	15 mo	Death; H & P dysfunction	
9	10	13	Y; H(a), L	LN, Ot, S	UH(LN)	VBL/MTX	1 mo	Death; H & L dysfunction	
10	11	11	N	B (skull)	n/a	VBL/MTX/PDN/CLB	26 mo	Alive; 8 yo	Chronic diarrea
11	11	17	Y; R	Maln, S	UH(S)	VBL/PDN	2 mo	Death; P dysfunction	
12	12	14	N	B (mandible), ST	FH(G)	PDN/CLB	32 mo	Alive; 15 yo	
13	12	24	Y; H(a,l,t), P	B (skull, femur, radius), Maln	UH(BM)	VCR/PDN/VBL/CLB/MTX CLB/MTX	2 mo	Death; H dysfunction	

See Table I for abbreviations.

TABLE III. Group C, 13–18 Months

Pt. #	Age S & S noted (mo)	Age dx (mo)	Presence of organ dysfunction	Involvement of other organs	Biopsy	Therapy	Length of therapy	Actual status	Late sequelae
1	13	18	Y; H(l)	B (skull, iliac, vertebrae, ischion, humerus, femur), LN, maln, S	UH(LN)	VBL/PDN/CLB/MTX	24 mo	Death; H dysfunction	
2	13	24	Y; H(t), L	B (skull, vertebrae), LN Maln, Ot, S	DH(LN)	No therapy	0 mo	Death; progressive disease	
3	13	17	Y; H(a), L, P	D.I., GI, LN, S	UH(LN)	VBL/PDN	24 mo	Death; H, L & P dysfunction	
4	13	25	Y; H(a)	B (skull, T-8 compression, femur), LN, N, S	DH(B)	VBL/PDN	1 mo	Death; progressive disease, visceral infiltration, gram-positive cocci sepsis	
5	14	16	Y; H(a), P	LN, S	DH(LN)	VBL/PDN	3 mo	Death; P dysfunction	
6	14	16	Y; H(a)	B (skull), Ot, ST	FH(S)	VBL/PDN/CLB/MTX CYT/VBL/PDN/PCZ VP-16/CLB/MTX XRT 24 Gy skull	14 mo 5 mo 12 mo	Alive; 9 yo	Dental hypoplasia & oral cavities, D.I., cholesteatoma, left hypoacusia
7	15	15	Y; H(a), L, P	B (skull, tibia), LN, Maln, Ot, S	UH(S)	VBL/PDN	8 mo	Death; L & P dysfunction	
8	15	15	Y; H(l,t), L, P	Ot, S	DH(S)	VBL/PDN/MTX/CLB	3 mo	Death; P dysfunction	
9	15	24	N	B (skull, palate), Ot, S	FH(S)	VCR/PDN/VBL/MTX/CLB	18 mo	Alive; 11 yo	Periodontal disease
10	17	20	Y; H(a)	Ot, S	FH(LN)	VCR/MTX/PDN	2 mo	Death; CNS infection, *L. monocytogenes*, had active disease	

(continued on overleaf)

TABLE III. Group C, 13–18 Months (continued from previous page)

Pt. #	Age S & S noted (mo)	Age dx (mo)	Presence of organ dysfunction	Involvement of other organs	Biopsy	Therapy	Length of therapy	Actual status	Late sequelae
11	17	17	Y; H(a), L	B (skull, pelvis, long bones) S	FH(S)	VBL/PDN/MTX/CLB	18 mo	Alive; 9 yo	Acetabular dysplasia Skull deformity
12	18	18	N	B (mandible), S, ST	FH(LN)	XRT 3560 cGy (maxilla/neck)		Alive; 17 yo	Face deformity Oligodonthia
13	18	26	N	B (skull, ribs), Ot, S, ST	FH(LN)	VCR/MTX/PDN/CLB	18 mo	Alive; 16 yo	
14	18	36	N	B (skull), D.I., S	FH(B)	VBL/PDN/MTX/CLB	18 mo	Alive; 17 yo	Endocrine: D.I., hypothyroidism, low stature
15	18	18	Y; H(a)	D.I., LN	FH(LN)	VBL/PDN/MTX/CLB	18 mo	Alive; 12 yo	D.I.
16	18	30	N	B (skull), D.I., ST	DH(ST)	VBL/PDN/CLB/MTX	18 mo	Death; postsurgical complication	
17	18	25	Y; H(a)	B (iliac), ST	DH(ST)	VBL/PDN/CLB/MTX		Alive; 8 yo	Orthopedic pathology
18	18	19	N	B (pelvis), S	DH(S)	VBL/PDN/CLB/MTX BLEO/CYT/VCR/ PDN/ADR XRT 1600 cGy	23 mo 9 cycles	Alive; 7 yo	R facial asymmetry, emotional instability
19	18	23	Y; H(a), L, P	LN, Maln, S	UH(LN)	VBL/PDN	2 mo	Death; H, L & P dysfunction	

See Table I for other abbreviations.

TABLE IV. Group D, 19–24 Months

Pt. #	Age S & S noted (mo)	Age dx (mo)	Presence of organ dysfunction	Involvement of other organs	Biopsy	Therapy	Length of therapy	Actual status	Late sequelae
1	20	23	Y; H(a)	B (skull, iliac, femur), LN, hepato/splenomegaly, vertebral collapse	FH(LN)	VBL/PDN/VCR/CLB	18 mo	Alive; 13 yo	Myoclonia, orthopedic
2	21	21	N	B (iliac)	FH(B)	XRT (2,000 cGy)		Alive; 11 yo	Vascular pelvis, slow dental eruption
3	22	24	Y; H(t), L	B (ischion, skull, spine, femur), LN, S	UH(LN)	CLB/PDN	3 mo	Death; H & L dysfunction	
4	22	22	Y: H(a,l,t), P	B (skull), S	DH(S)	PDN/VBL/VCR/CYT/Ara C	4 mo	Death; H dysfunction & polimicrobial Gram-negative sepsis	
5	23	27	Y; H(a), L	B (skull, humerus, femur, ribs) D.I., LN, Ot, S	UH(LN)	VBL/PDN	7 mo	Death; L dysfunction	
6	23	26	N	B (acetabulum, skull, iliac ribs)	FH(B)	VBL/PDN	18 mo	Alive; 8 yo	
7	24	30	Y; H(a), P	B (skull, iliac, ribs, femur humerus), GI, Maln, S, ST	UH(LN)	VBL/PDN/CYT/VCR/CLB/MTX	12 mo	Death; H & P dysfunction	

See Table I for abbreviations.

thrombocytopenia (platelet count <100,000 platelets/mm^3); (2) hepatic dysfunction: hypoproteinemia (total protein <5.5 g/dl or albumin <2.5 g/dl), edema, ascites, and/or hyperbilirubinemia (total bilirrubin >1.5 g/dl, not attributable to hemolysis); (3) pulmonary dysfunction: presence of tachypnea and/or dyspnea, cyanosis, cough, pneumothorax, or pleural effusion attributable to the disease. Kaplan-Meier survival curves [30] were used to evaluate disease-free survival, with a minimal follow-up time of 5 years after diagnosis and initiation of therapy.

Forty-five patients were enrolled in the following chemotherapy protocol [8]:

Induction

Prednisone (PDN) 50 mg/m^2 PO qd × 6 weeks and taper
Vinblastine (VBL) 6 mg/m^2 IV q week × 8 weeks or
Vincristine (VCR) 2 mg/m^2 IV q week × 8 weeks

Maintenance

Chlorambucil (CLB) 0.1 mg/kg PO q day × 18 months, starting week 7

Methotrexate (MTX) 40 mg/m^2 PO q week × 18 months, starting week 7

Pseudo/re-induction

VBL 6 mg/m^2 IV q 6 weeks, starting week 12 for 18 months

PDN 60 mg/m^2 PO qd for 2 weeks q 6 weeks, starting week 12 for 18 months

Of the remaining 10 evaluable patients, 2 patients who failed to respond to initial chemotherapy received VP-16, and 1 patient was initially treated with thymosin extract and then followed the chemotherapy regime outlined earlier. Two patients received radiation therapy only, and five patients received varying combinations of vinca alkaloid and steroids plus cytarabine, procarbazine, and cyclophosphamide. The pathologic reports of the biopsied organs were reviewed for the presence of favorable (FH) or unfavorable (UH) histology according to Newton and Hamoudi's parameters [31], and were correlated with the clinical outcome of our patients.

RESULTS

Of the initial 65 patients, 10 were lost to follow-up. The remaining 55 evaluable patients had a male-to-female ratio of 1.2:1.0. Twenty of these children (36.3%) remain alive, although varying degrees of sequelae persist in approximately 80% of the patients (Tables I–IV).

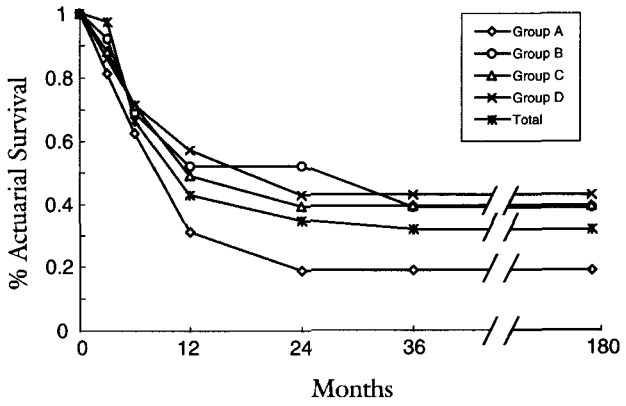

Fig. 1. Langerhans cell histiocytosis. Actuarial survival in children under 2 years of age.

The breakdown of survival for age is as follows: In group A (0–6 months), 3 out of 16 patients are alive (18.7%); in group B (7–12 months), 5 out of 13 patients are alive (38.4%); in group C (13–18 months), 9 out of 19 patients (46.1%) are alive; and in group D (19–24 months), 3 out of 7 patients are alive (42.8%). The Kaplan-Meier actuarial survival curve shows an 8 year, 31.8% disease free survival. There is no statistical significant difference between the groups (Fig. 1).

The initial clinical presentation relating the presence or abscence of organ dysfunction to outcome is shown in Table V. Patients presenting without organ dysfunction are as follows: In group A, three patients (19%) initially presented without evidence or organ dysfunction, but all of them had skin involvement. In two patients the disease progressed to organ dysfunction and death; the third-patient died of therapy-related sepsis. In group B, of five patients (38.4%) showing no dysfunction at diagnosis, four of them are alive. In group C, six patients (31.5%) had no evidence of initial organ dysfunction, and only one patient died of complications resulting from surgery. In group D, two patients (28.5%) had no organ dysfunction at diagnosis and both are alive. Overall, 16 patients (29%) had no organ dysfunction at diagnosis, and 11 patients (69%) are alive.

Those who presented with dysfunction are as follows: In group A, (Tables I and V), five patients (31%) had dysfunction in one organ at presentation. Three patients with hematologic dysfunction (isolated anemia) are alive, while the patients with isolated pulmonary (one) or hepatic (one) dysfunction are dead. All of the remaining eight patients with dysfunction in two or three organs did not survive. In this age group, 81% of the patients died; among the causes of death were progressive organ dysfunction (7/13), organ dysfunction and sepsis (3/13), sepsis (2/13), and sepsis secondary to chemotherapy (1/13). Ten of the 13 patients had unfavorable histology (UH), and 9 of these are dead. The average time between the patient's noting the initial signs/symptoms and diagnosis was ~6 months (0–21 mo). Fifteen of the 16 patients in group A were enrolled in the chemotherapy protocol, and the mean time of therapy was ~4 months (1–14 months), with a poor response to therapy.

In Group B, (Tables II and V), 5 of 13 patients (38%) presented without organ dysfunction. One patient progressed to hematologic and respiratory dysfunction and subsequently died. The remaining four patients are alive and disease-free. Seven patients (62%) presented with dysfunction of two or three organs at diagnosis. Six of these patients are dead, and only one patient with hepatic and respiratory dysfunction remains alive. The average time between the patient's noticing the initial signs/symptoms and diagnosis was ~7 months (0–27 months). Eleven of the 13 patients were enrolled in the protocol; 6 of these patients died before completing 3 months of therapy. The causes of death were progressive organ dysfunction in six patients, organ dysfunction and sepsis in one patient, and sepsis in one patient. Five patients had UH, and all of these have died.

In Group C (Tables III and V), six patients presented without organ dysfunction, and five of these are alive. Six patients presented with dysfunction in one organ (hematologic), and three of these are alive. Seven patients presented with dysfunction in two or more organs, and the mortality rate in this group was 86%; all patients with respiratory involvement are dead, and only one patient with hematologic and hepatic dysfunction is alive. The causes of death were organ dysfunction in seven patients, organ dysfunction and sepsis in one patient, chemotherapy and surgical complications in one patient, and *L. monocytogenes* CNS infection in one patient. The average time between the initial signs/symptoms and diagnosis was ~5 months (0–18 months). Sixteen of the 19 patients were enrolled in the protocol, and 10 patients in this group died; six of them received less than 4 months of therapy. Seven of the pathologic reports were descriptive of LCH; eight reports showed favorable histology (FH), and seven of these patients are alive; and all four patients whose report showed UH are dead. All eight patients who completed therapy and one who received radiation-only therapy are alive.

In Group D (Tables IV and V) the mortality associated with dysfunction of two organs was 100%. The cause of death was organ dysfunction in three patients and organ dysfunction/sepsis in one patient. The average time between detecting the initial signs/symptoms and diagnosis was ~2 months (0–6 months). Three patients were enrolled in the protocol, and one of them is alive. One surviving patient received prednisone and vinblastine (PDN/VBL) as the only chemotherapy regime, and another surviving patient received solely radiation therapy. UH was reported in three patients, all of whom are dead.

Among other clinical observations, several degrees of severe and moderate malnutrition were present in 10 patients, all of whom died. Gastrointestinal involvement

TABLE V. Initial Presentation and Outcome Related to Organ Dysfunction

	A 0–6 months		B 7–12 months		C 13–18 months		D 19–24 months		Total		
Dysfunction	Pat (%)	Death	Pat (%)	Death	Pat (%)	Death	Pat (%)	Death	Pat (%)	Death	Alive
No organ	3 (19)	3	5 (38)	1	6 (32)	1	2 (29)	0	16 (29)	5 (31)	11
One organ											
Hematologic (H)	3 (19)	0	0	0	6 (32)	3	1 (14)	0	10 (18)	3	7
Hepatic (L)	1 (6)	1	0	0	0	0	0	0	1 (2)	1	0
Respiratory (P)	1 (6)	1	1 (8)	1	0	0	0	0	2 (4)	2	0
									13 (24)	6 (46)	7
Two/three organs											
H & L	5 (31)	5	3 (31)	3	2 (11)	1	2 (29)	2	12 (24)	11	1
H & P	1 (6)	1	2 (15)	2	1 (5)	1	2 (29)	2	6 (11)	6	0
L & P	0	0	1 (8)	0	0	0	0	0	1 (2)	0	1
H, L & P	2 (13)	2	1 (8)	1	4 (21)	4	0	0	7 (13)	7	0
									26 (47)	24 (92)	2
Total	16	13 (82%)	13	8 (62%)	19	10 (53%)	7	4 (57%)	55 (100%)	35 (63.6%)	20(36.3%)

TABLE VI. Initial Clinical and Laboratory Presentation of Surviving Patients

	Group A	Group B	Group C	Group D	Total
Signs					
Bone lesion	3/3	5/5	8/9	3/3	19/20
Dermatitis	2/3	2/5	6/9	—	10/20
Fever	1/3	3/5	5/9	1/3	10/20
Soft tissue mass	2/3	4/5	3/9	—	9/20
Otitis	—	2/5	2/9	—	4/20
Exophthalmos	—	1/5	2/9	—	3/20
Symptoms					
Malaise	—	2/5	3/9	2/3	7/20
Limp	—	1/5	3/9	2/3	6/20
Diabetes insipidus	1/3	1/5	1/9	—	3/20
Pain	—	1/5	—	1/3	2/20
Laboratory data					
Anemia	3/3	—	3/9	1/3	7/20
Leukocytosis	2/3	2/5	3/9	1/3	8/20
Thrombocytosis	1/3	—	3/9	—	4/20
Pathology/histology report					
Favorable	2/3	3/5	7/9	3/3	15/20
Unfavorable	1/3	—	—	—	1/20

was present in four patients, all of whom are dead [32, 33]. The presence of thrombocytopenia at diagnosis (n = 9) resulted in 100% mortality. It was associated with leukopenia and/or anemia in seven of nine patients, and with hepatic dysfunction in the remaining two patients. The cause of septic deaths included *Staphylococcus*, gram-negative bacilli (*Salmonella*, *Pseudomonas*, *coliforms*), and *Listeria*.

The clinical and laboratory pathology present in the surviving population of patients is summarized in Table VI. Forty-nine pathologic reports were reviewed: 13 were descriptive of LCH, 22 showed UH, and 14 showed FH. Twenty-one of the patients with UH died, while 13 patients with FH are alive. The most common late sequelae of the disease and therapy are endocrine, orofacial, and orthopedic pathologies (Tables I–IV) [34]. In summary, of 55 evaluable patients, 20 patients (36%) survived 5–15 years from the initial diagnosis. Five of 16 patients (31%) without organ dysfunction died, and 30 of 39 patients (77%) with organ dysfunction died. This difference was highly significant ($P < 0.005$).

DISCUSSION

In 1953, Lichtenstein combined eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease into a single pathologic entity that he named histiocytosis X [4]. In 1962, Lahey [5] developed a scoring pattern for organ involvement and disease dissemination relative to outcome, and in 1975 he expanded that pattern further [6]. The first detailed analysis of disease parameters, including age, was carried out in 1981 by Greenberger et al.[7]. They studied 127 patients with histiocytosis X and divided them according to age and organ involvement. In this study, infants less than 2 years

of age with multiple organ involvement had significantly greater mortality than the older age groups.

In this report we focused on two patient outcome parameters: age and initial organ dysfunction at diagnosis. Although the age group was not statistically significant in this study, higher mortality (81.3%), was nevertheless seen in the 0–6 month age group (Fig. 1). Patients who at diagnosis initially presented with organ dysfunction had a mortality of 31%, patients who presented with dysfunction in one organ had a mortality of 46%, and patients with initial dysfunction of two or three organs had a mortality of 92% (Table V).

The presence of thrombocytopenia has been previously shown to be associated with poor outcome [5,29]. In this study, the presence of respiratory dysfunction or thrombocytopenia was significantly related to mortality (>90%). Indeed, 18% of the patients, all of whom died, had thrombocytopenia, either alone or in combination with other hemotologic manifestations of disease (anemia and/or leukopenia) or with hepatic dysfunction. The major cause of death was progressive disease leading to organ failure.

Dermal involvement alone in younger ages has been considered an unfavorable prognostic factor [41]. Three patients in group A and one patient in group B initially presented with skin involvement and without organ dysfunction. Three of these patients progressed to organ dysfunction and subsequently died from organ failure (Tables I–IV). Recent studies [28] support the fact that a poor or null response to initial therapy is highly correlated with mortality. This finding was reflected in our study in which the medial length of therapy was ~2–4 months in patients with dysfunction of two or three organs. The reason for the lack of response to therapy in our population remains unclear. Widespread disease involvement combined with the delay in diagnosis and initiation of therapy, lower tolerance for chemotherapy in younger ages, and malnutrition may all be important factors to consider. At the present time, another class of therapeutic agents, the epipodophyllotoxins (VP-16), in combination with conventional therapy (vinblastin and prednisone), is being evaluated [26–28]. Cyclosporine A, anti-thymocyte globulin, bone marrow transplantation, and liver transplantation have been used successfully in refractory and isolated cases [15,35–40].

The presence of bone lesions (with or without associated symptoms), soft tissue masses, and/or dermatitis at diagnosis was more frequently seen in patients without organ dysfunction and in the group of patients 12–24 months of age. These patients also demonstrated a favorable response overall to therapy. The sole presence of bone involvement is considered to be a favorable prognositic feature [41], and this was confirmed in our study. Among the laboratory observations noted, thrombocytosis at diagnosis was present in 20% of the surviving patients. (Table VI), as compared with patients who presented with thrombocytopenia. As in earlier studies, in our study the presence of a favorable histology was related to good outcome, while the presence of an unfavorable histology was related to organ dysfunction and a poor outcome [6,31].

We have followed the study population for 5–15 years off therapy. As noted in past studies, the natural history of the disease and the late sequelae of therapy included endocrine, orofacial, and osseous pathologies [42–46]. At the present time, secondary malignancies have not been observed [7,47,48]. Although recent reports on the presence of clonality in LCH support a neoplastic etiology [21,22], the biology and pathophysiology of this enigmatic disease remains poorly understood.

In summary, this study supports earlier data indicating a 31.8% survival in infants less than 2 years of age at diagnosis [49,50]. Higher mortality was present in the younger ages, the presence or absence of initial organ dysfunction has a strong correlation with outcome, the use of conventional therapy in widespread disease had a very poor initial response, and the long-term survivors have suffered late sequelae, with a high morbidity requiring continuous medical attention.

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